A Chronic Toxicity and Carcinogenicity Study in Rats Administered Diaphragm Valve and Plug Assembly, Leaf Valve and Overlay Assembly and Patch and Overlay Assembly by Subcutaneous Implantation

CONCLUSIONS

The subcutaneous implantation of the three test articles (Valve/Plug, Valve/Overlay or Patch/Overlay) resulted in an inflammatory reaction at the implant site as evidenced grossly by edema and eschar, and, occasionally, erythema, ulceration and discharge. After 12 months, 18 months and after two years of implantation, the lesions observed at the implant sites were microscopically similar for all three of the implanted test articles. The implant site findings consisted of multiloculated cyst-like areas (test article particles) surrounded by thin fibrous capsules and in some animals, interstitial fibrosis penetrating between the particles. Macrophage aggregates and multinucleated foreign body giant cells, pigment-laden macrophages, and mononuclear cell infiltrates were also noted. The implant sites of the Sham Control group animals were not apparent in most animals except for focal scar areas of dermal fibrosis.

Masses were grossly observed at the implant sites of several animals in the test article implanted groups during the study. The implant site masses were later histologically diagnosed primarily as fibrosarcomas, or to a lesser degree, as undifferentiated sarcoma, osteosarcoma, fibroma histiocytic sarcoma, malignant fibrous histocytoma or chordoma. The histocytic sarcomas and malignant fibrous histocytomas were considered systemic in origin and not test article related. The chordoma was postulated to have arisen from the spinal cord underlying the implant site. The other implant site neoplasms (fibrosarcoma, undifferentiated sarcoma, osteosarcoma, and fibroma) observed in these animals are those that are commonly found following the subcutaneous implantation of inert solid materials of many types, sizes and shapes in rodents[1-12]. The test articles were pulverized and dispersed into a large subcutaneous surgical pocket encompassing the entire dorsal region, down the shoulders, along the flanks and over the outer surface of the thighs in order to maximize surface area and minimize the development of foreign body sarcoma formation. Generally, each test article was uniformly distributed, but clumping of the test article did occur in small localized areas, especially along the most ventral regions of the surgical pocket. Consequently, areas of test article formed which are believed to have been of sufficient density to be recognized as solid objects, ultimately resulting in solid state type carcinogenicity. Pulverization and dispersal of the fragments of test articles over a large area appeared to have limited, but not eliminated, the number of subcutaneous sarcomas that were seen.

As discussed in the pathology reports, the other histopathology findings, including mononuclear cell leukemia, pituitary adenoma, mammary gland fibroadenoma, uterine endometrial stromal polyps and subcutaneous tissue neoplasms of mesenchymal origin observed in the Sham Control and test article groups were of the type and incidence typical for female Fischer 344 rats. Survival time and time-to-death were not statistically different in the test article groups when compared to the Sham Control group. Time-to-tumor was significantly shorter in the test article groups compared to the Sham Control group. The decreased time-to-tumor for the test article groups is considered a result of the solid state carcinogenicity that developed in the implant sites of the test article groups.

Based on the results of a number of parameters including body weight data, general health data, clinical pathology analyses, organ weight data, survival data and histopathological evaluation of tissues, there was no indication of systemic toxicity or carcinogenicity (with the exception of solid state carcinogenicity) as a result of the subcutaneous implantation of the three pulverized test articles after 2 years of exposure.

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